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(19)(CA) **APPLICATION FOR CANADIAN PATENT** (12)

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(54) Cyclic Amine Derivatives

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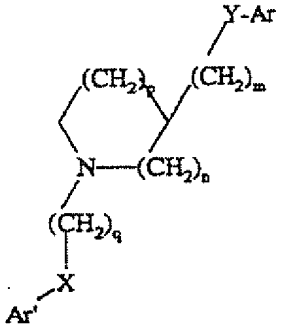
Cyclic amine derivatives

The invention relates to novel cyclic amine derivatives of the formula I



I,

in which

Ar and Ar' are each, independently of one another, phenyl which is unsubstituted or substituted once or twice by NO_2, NH_2, Hal, CF_3, A, $NHSO_2A$ or NHAc,

X and Y are each, independently of one another, O or a bond,

m is 0 or 1,

n is 0, 1 or 2,

p is 0, 1, 2 or 3,

q is 2 or 3,

A is alkyl having 1-6 C atoms,

Hal is F, Cl, Br or I and

Ac is alkanoyl having 1-8 C atoms, aralkanoyl having 8-10 C atoms or aroyl having 7-11 C atoms,

and their physiologically acceptable salts.

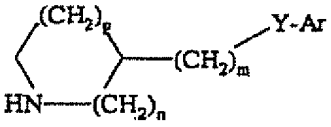
The invention was based on the object of finding novel compounds which can be used for the production of medicaments.

It has been found that the compounds of the formula I and their physiologically acceptable acid addition salts have valuable pharmacological properties while being well tolerated. Thus, in particular, they show antiarrhythmic effects and positive inotropic effects prolonging the refractory period of the heart.

The cardiac action can be measured, for example, on anaesthetized or conscious rats, guinea pigs, dogs, cats, monkeys or minipigs, and the positive inotropic effect can also be measured on isolated heart preparations (for example atrium, papillary muscle or perfused whole heart) of rats, guinea pigs, cats or dogs, for example by methods as described in Arzneimittelforschung, volume 31 (I) No. 1a (1981), pages 141 to 170, or by Schliep et al. in the 9th International Congress of Pharmacol., London (1984), Abstracts of papers 9P.

The compounds can therefore be used as pharmaceutical active substances in human and veterinary medicine. They can furthermore be used as intermediates for preparing other pharmaceutical active substances.

The invention accordingly relates to the compounds of the formula I, to their acid addition salts and to a process for their preparation, characterized in that a compound of the formula II



II,

in which

Ar, Y, m, n and p have the stated meaning,

is reacted with a compound of the formula III,

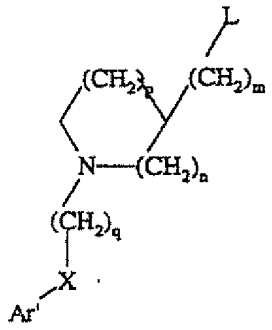
$$Ar\text{-}X\text{-}(CH_2)_q\text{-}L \qquad III,$$

in which

Ar, X and q have the stated meaning, and

L is OH, Cl, Br or a reactive, functionally modified OH group,

or in that, to prepare a compound of the formula I according to Claim 1 in which Y is oxygen, a compound of the formula IV



IV,

in which

Ar', X, L, m, n, p and q have the stated meanings,

is reacted with a compound of the formula V

$$Ar\text{-}Z \qquad V,$$

in which

Ar has the stated meaning, and

Z is OH or a reactive, functionally modified OH group,

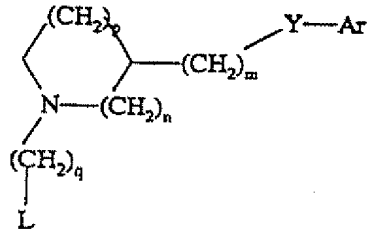
including a group with salt-like characteristics,

or in that a compound of the formula Va

Ar'-Z Va,

in which Ar' and Z have the stated meanings,

is reacted with a compound of the formula VI



VI,

in which

Ar, Y, L, m, n, p and q have the stated meanings,

or in that a compound which corresponds to the formula I but has in place of one or more CH_2 groups one or more reducible groups is converted by reduction into a compound of the formula I, and/or in that one or both groups Ar and Ar' in a compound of the formula I are converted into other radicals Ar and Ar', respectively, and/or in that a basic compound of the formula I is converted by treatment with an acid into one of its physiologically acceptable acid addition salts.

Hereinbefore and hereinafter, Ar, Ar', A, Hal, L, X, Y and Z as well as the parameters m, n, p and q have the meanings stated for the formulae I, III and V unless expressly stated otherwise.

The radical A is alkyl having 1, 2, 3, 4, 5 or 6, in particular 1, 2 or 3, C atoms, preferably methyl, as well as ethyl, n-propyl, isopropyl, n-butyl, isobutyl,

sec-butyl or tert-butyl. A in $NHSO_2A$ is preferably methyl.

The group Ac is preferably alkanoyl having 1-8 C atoms, in particular having 1, 2, 3, 4 or 5 C atoms; specifically, Ac is preferably acetyl, furthermore preferably formyl, propionyl, butyryl, isobutyryl, valeryl, isovaleryl, pivaloyl (trimethylacetyl), furthermore preferably unsubstituted or optionally substituted aroyl having 7-11 C atoms, suitable substituents being, in particular, 1-3, preferably one, of the following groups: alkyl, alkoxy, alkylthio, alkylsulfinyl or alkylsulfonyl having, in each case, 1-3, preferably 1 or 2, C atoms, methylenedioxy, furthermore OH, F, Cl, Br, I, NO_2, NH_2, alkylamino or dialkylamino having, in each case, 1-3, preferably 1 or 2, C atoms in the alkyl group. Individual preferred aroyl radicals are benzoyl, o-, m- or p-toluyl, o-, m- or p-methoxybenzoyl, 2,3-, 2,4-, 2,5-, 2,6-, 3,4- or 3,5-dimethoxybenzoyl, 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6- or 3,4,5-trimethoxybenzoyl, o-, m- or p-methylthiobenzoyl, o-, m- or p-methylsulfinylbenzoyl, o-, m- or p-methylsulfonylbenzoyl, 2,3- or 3,4-methylenedioxybenzoyl, 1- or 2-naphthoyl. Ac may furthermore be aralkanoyl having 1-10 C atoms such as, for example, phenylacetyl, 2- or 3-phenylpropionyl or 2-, 3- or 4-phenylbutyryl.

NHAc is particularly preferably acetamido.

If one of the compounds of the formulae I to VI contains several groups A and/or Ac it is possible for the groups of the same type in each case to be identical to or different from one another.

The radicals Ar and Ar' are each, independently of one another, unsubstituted or mono- or disubstituted phenyl, but the two radicals preferably have the same substitution pattern. When they are monosubstituted, the appropriate substituent is preferably in the para position.

Particularly preferred substituents on the phenyl radical are $-NH_2$, $-NO_2$, $-NHSO_2CH_3$ or $-NHCOCH_3$.

Y is preferably oxygen, while X is preferably a bond.

The variable m is preferably 1, q is preferably 2, whereas n is particularly preferably 1 or 0 and p is 1, 2 or 3.

Accordingly, the invention particularly relates to those compounds of the formula I in which at least one of the said radicals has one of the meanings mentioned above, especially one of the preferred meanings mentioned above.

Some preferred groups of compounds can be expressed by the following part-formulae Ia to Ig, which correspond to the formula I and in which the undefined radicals and parameters have the meaning stated for formula I but in which

in Ia Ar and Ar' are each p-methylsulfonamidophenyl;

in Ib Ar and Ar' are each p-nitrophenyl;

in Ic Ar and Ar' are each p-aminophenyl;

in Id n = 2 and p = 1 so that the heterocyclic group is a piperidine radical;

in Ie n = 1 and p = 3 so that the heterocyclic group is a hexahydroazepine radical;

in If n = 0 and p = 2 so that the heterocyclic group is a pyrrolidine radical;

in Ig q = 2 and m = 0, and n and p have the meanings stated in Id to If.

Further preferred compounds are those of the

part-formulae Ih and Iah to Igh which correspond to the part-formulae I and Ia to Ig but in which additionally Y is oxygen and X is a bond.

The compounds of the formula I are moreover prepared by methods known per se, as described in the literature (for example in the standard works such as Houben-Weyl, Methoden der Organischen Chemie [Methods of Organic Chemistry], Georg-Thieme-Verlag, Stuttgart or J. March, Adv. Org. Chem., 3rd Ed., J. Wiley & Sons, N.Y. (1985)), specifically under reaction conditions which are known and suitable for the said reactions. It is moreover possible to make use of variants which are known per se but which are not mentioned in detail here.

The starting materials for the claimed process can, if required, also be formed in situ in such a manner that they are not isolated from the reaction mixture but immediately reacted further to give the compounds of the formula I.

Some of the starting materials of the formula II and III are known. Those which are unknown can be prepared by methods known per se. The compounds of the formula II in which Y is oxygen are prepared, for example, starting from compounds which correspond to the formula II per se but, in place of the radical -Y-Ar, contain, for example, an OH group, a reactive functionally modified OH group, Cl or Br and whose secondary N atom is blocked by a protective group known per se, by reaction with phenol or with a substituted derivative or with a corresponding phenolate under conditions as are known per se for ether synthesis, but especially under the conditions of the Mitsonubo reaction (J. Am. Chem. Soc. 104, 6876 (1982)).

Furthermore, certain compounds of the formula II (Y = a bond) can also be prepared, for example, starting from benzylpyrrolidines or -piperidines or phenylpyrrolidines or -piperidines by substitution on the aromatic system, in particular nitration, where appropriate with

subsequent reduction and further derivatization.

The substituted phenyl compounds of the formula II are, as a rule, known or can easily be prepared in analogy to the known compounds.

The reaction of the compounds II and III takes place by methods as are known from the literature for the alkylation of amines. It is possible for the components to be melted together in the absence of a solvent, where appropriate in a closed tube or in an autoclave. However, it is also possible to react the compounds in the presence of an inert solvent. Examples of suitable solvents are hydrocarbons such as benzene, toluene, xylene; ketones such as acetone, butanone; alcohols such as methanol, ethanol, isopropanol, n-butanol; ethers such as tetrahydrofuran (THF) or dioxane; amides such as dimethylformamide (DMF) or N-methylpyrrolidine; nitriles such as acetonitrile, where appropriate also mixtures of these solvents with one another or mixtures with water. The addition of an acid acceptor, for example an alkali metal or alkaline earth metal hydroxide, carbonate or bicarbonate or of another alkali metal or alkaline earth metal salt of a weak acid, preferably of potassium, sodium or calcium, or the addition of an organic base such as triethylamine, dimethylaniline, pyridine or quinoline or of an excess of the amine component, may be beneficial. The reaction time depends on the conditions employed and is between a few minutes and 14 days, and the reaction temperature is between about 0 and 150°, normally between 20 and 130°.

It is furthermore possible for the preparation of a compound of the formula I in which Y is oxygen to react a compound of the formula IV with a benzene derivative of the formula V.

Compounds of the formula IV can be obtained, for example, by reacting cyclic amines such as, for example,

piperidinols, pyrrolidinols, prolinols or else cyclic amines which are substituted by a hydroxymethyl or halomethyl group, where halogen is preferably chlorine or bromine, with a phenylalkyl bromide or chloride (alkyl = ethyl or propyl) or phenoxyalkyl bromide or chloride, where the aromatic system can also be substituted by one or two of the radicals stated for Ar, so that N-alkylation takes place.

The benzene derivatives of the formula V are known as a rule and can be prepared by the methods known per se for aromatic substitution.

The reaction of the compounds of the formula IV with those of the formula V takes place under conditions typical for synthesizing ethers. Suitable solvents are those mentioned above for the reaction of II with III. Likewise, the same reaction times and temperatures are suitable. Particularly preferred reaction conditions are those of the Mitsonubo reaction, using azodicarboxylic diester and triphenylphosphine if a compound of the formula I with Y = oxygen is to be prepared.

It is noteworthy that in the reaction of IV with V under "Mitsonubo conditions" there may be a rearrangement with ring contraction or ring expansion by in each case one C atom of the cyclic amine unit so that, for example, a piperidine derivative may be produced from a pyrrolidine derivative or a hexahydroazepine derivative may be produced from a piperidine derivative, or else conversely a pyrrolidine system may be produced from a piperidine system.

Resulting product mixtures of five- and six-membered rings or six- and seven-membered heterocycles can easily be separated by preparative chromatography on silica gel.

Furthermore, compounds of the formula I can also be prepared by reacting benzene derivatives of the

formula Va with cyclic amines of the formula VI. The compounds of the formula Va are known per se or can be prepared in analogy to methods known per se, for example by those of aromatic electrophilic substitution.

Compounds of the formula VI can be prepared, for example, starting from the particular cyclic amine by etherification of the free hydroxyl group on the side chain as well as N-alkylation of the heterocycle, where appropriate after elimination of a necessary protective group under the conditions stated above for the preparation of the compounds of the formula II using those of the formula III.

The reaction of the compounds Va with the substances of the formula VI takes place in analogy to the reaction of IV with V as stated above, although no rearrangements take place in this case.

It is furthermore possible to obtain a compound of the formula I by reducing a compound which corresponds to the formula I but contains, in place of one or more CH_2 groups, one or more reducible groups, preferably at temperatures between -80 and +250° in the presence of at least one inert solvent.

Reducible (hydrogen-replaceable) groups are, in particular, oxygen in a carbonyl group, hydroxyl, arylsulfonyloxy (for example p-toluenesulfonyloxy), N-benzenesulfonyl, N-benzyl or O-benzyl.

It is possible in principle to convert compounds which contain only one, or those which contain two or more of the abovementioned groups side by side, by reduction into a compound of the formula I. Preferably used for this purpose is nascent hydrogen or complex metal hydrides, furthermore reductions with gaseous hydrogen with catalysis by transition metals.

If nascent hydrogen is used as reducing agent, it can be generated, for example, by treating metals with weak acids or with bases. Thus, for example, a mixture of zinc with alkali metal hydroxide solution or of iron with acetic acid can be used. Also suitable is the use of sodium of another alkali metal in an alcohol such as ethanol, isopropanol, butanol, amyl or isoamyl alcohol or phenol. It is furthermore possible to use an aluminium/nickel alloy in alkaline aqueous solution, where appropriate with the addition of ethanol. Sodium or aluminium amalgam in aqueous/alcoholic or aqueous solution is also suitable for generating nascent hydrogen. The reaction can also be carried out in heterogeneous phase, in which case an aqueous and a benzene or toluene phase is preferably used.

It is furthermore particularly advantageous to use complex metal hydrides such as $LiAlH_4$, $NaBH_4$, diisobutylaluminium hydride or $NaAl(OCH_2CH_2OCH_3)_2H_2$ as well as diborane as reducing agents, if required with the addition of catalysts such as BF_3, $AlCl_3$ or LiBr. Particularly suitable solvents for this purpose are ethers such as diethyl ether, di-n-butyl ether, THF, dioxane, diglyme or 1,2-dimethoxyethane as well as hydrocarbons such as benzene. Solvents primarily suitable for a reduction with $NaBH_4$ are alcohols such as methanol or ethanol, as well as water and aqueous alcohols. Reduction by these methods preferably takes place at temperatures between -80 and +150°, in particular between about 0 and about 100°.

The -CO- groups in the amides can be reduced to CH_2 groups particularly advantageously with $LiAlH_4$ in THF at temperatures between about 0 and 66°.

It is furthermore possible to carry out certain reductions by using H_2 gas with the catalytic action of transition metals such as, for example, Raney Ni or Pd. It is possible in this way, for example, to replace Cl, Br, I, SH or, in certain cases, also OH groups by

hydrogen. Likewise, nitro groups can be converted, for example, by catalytic hydrogenation with Pd/H_2 in methanol into NH_2 groups.

Furthermore, one compound of the formula I can be converted by methods known per se into a different compound of the formula I.

The phenyl rings in the compounds of the formula I can, if side reactions are to be precluded, for example be chlorinated, brominated or alkylated under the conditions of Friedel-Crafts reactions by reacting the appropriate halogen or alkyl chloride or alkyl bromide with catalysis by Lewis acids such as, for example, $AlCl_3$, $FeBr_3$ or Fe, at temperatures between 30° and 150°, preferably between 50° and 150°, in an inert solvent such as, for example, hydrocarbons, THF or tetrachloromethane, with the compound of the formula I which is to be derivatized.

It is furthermore possible to convert a compound of the formula I in which Ar or Ar' is substituted by NH_2 by alkylation or acylation by methods which are generally customary and known for amines into corresponding compounds of the formula I in which Ar or Ar' is substituted by NHA or NHAc.

A resulting base of the formula I can be converted with an acid into the relevant acid addition salt. Acids suitable for this reaction are those which provide physiologically acceptable salts. Thus, it is possible to use inorganic acids, for example sulfuric acid, hydrohalic acids such as hydrochloric acid or hydrobromic acid, phosphoric acids such as orthophosphoric acid, nitric acid, sulfamic acid, also organic acids, specifically aliphatic, alicyclic, araliphatic, aromatic or heterocyclic mono- or polybasic carboxylic, sulfonic or sulfuric acids, such as formic acid, acetic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic

acid, lactic acid, tartaric acid, malic acid, benzoic acid, salicylic acid, 2-phenylpropionic acid, citric acid, gluconic acid, ascorbic acid, nicotinic acid, isonicotinic acid, methane- or ethanesulfonic acid, ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalene mono- and -disulfonic acids and lauryl sulfuric acid.

The free bases of the formula I can, if required, be liberated from their salts by treatment with strong bases such as sodium or potassium hydroxide, sodium or potassium carbonate, as long as no other acidic groups are present in the molecule.

The compounds of the formula I may have a centre of asymmetry. They may therefore result from their preparation as racemates or, if optically active starting materials are used, also in optically active form. Resulting racemates can, if required, be resolved into their optical antipodes mechanically or chemically by methods known per se. Preferably, diastereomers are formed from the racemate by reaction with an optically active resolving agent.

Examples of suitable resolving agents are optically active acids such as the D and L forms of tartaric acids, dibenzoyltartaric acid, diacetyltartaric acid, camphosulfonic acids, mandelic acid, malic acid or lactic acid. The various forms of the diastereomers can be separated in a manner known per se, for example by fractional crystallization, and the optically active compounds of the formula I can be liberated from the diastereomers in a manner known per se.

It is furthermore possible to separate the enantiomers by preparative chromatographic methods known per se. Silica gel is preferred as stationary phase. Particularly preferred mobile phases are mixtures of ethyl acetate and heptane or dichloromethane and methanol.

The invention furthermore relates to the use of the compounds of the formula I and their physiologically acceptable salts for the production of pharmaceutical preparations, in particular by non-chemical means. For this purpose they can be converted together with at least one vehicle or ancillary substance and, where appropriate, in combination with one or more other active substance(s) into a suitable dosage form.

The invention furthermore relates to compositions, in particular pharmaceutical preparations, containing at least one compound of the formula I and/or one of its physiologically acceptable salts. These preparations can be used as medicaments in human and veterinary medicine. Suitable vehicles are organic or inorganic substances which are suitable for enteral (for example oral), parenteral or topical administration and which do not react with the novel compounds, for example water, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose or starch, magnesium stearate, talc, petrolatum. Tablets, coated tablets, capsules, syrups, solutions, drops or suppositories are used in particular for enteral administration, solutions, preferably oily or aqueous solutions, as well as suspensions, emulsions or implants are used for parenteral administration, and ointments, creams or powders are used for topical application. The novel compounds can also be lyophilized and the resulting lyophilizates used, for example, to produce products for injection.

The stated preparations can be sterilized and/or contain ancillary substances such as lubricants, preservatives, stabilizers and/or wetting agents, emulsifiers, salts to influence the osmotic pressure, buffer substances, colorants, flavourings and/or aromatizing substances. They can, if required, also contain one or more other active substances, for example one or more vitamins.

The compounds of the formula I and their physiologically acceptable salts can be used for the therapeutic treatment of the human or animal body and for controlling diseases. They are particularly suitable for the treatment of arrhythmias and tachycardias.

For this purpose the substances according to the invention are, as a rule, administered in analogy to known substances with antiarrhythmic activity, such as aprindine, flecainide or amiodarone, preferably in dosages between about 1 and 100 mg, in particular between 2 and 20 mg per dosage unit.

The daily dosage is preferably between about 0.02 and 2 mg/kg of body weight. The specific dose for each particular patient depends, however, on a wide variety of factors, for example on the efficacy of the specific compound used, on the age, body weight, general state of health, sex, on the diet, on the time and route of administration, on the rate of excretion, pharmaceutical combination and severity of the particular disorder to which the therapy applies. Oral administration is preferred.

In the following examples, "usual working up" means:

If necessary, water or dilute sodium hydroxide solution is added, extraction is carried out with an organic solvent such as ethyl acetate, chloroform or dichloromethane, the organic phase is separated off, dried over sodium sulfate, filtered and evaporated, and purification is carried out by chromatography on silica gel and/or crystallization. The optical rotations were measured in methanol (c = 1) unless stated otherwise. If the production of two substances is described in the individual examples, these are always separate from one another.

All temperatures are stated hereinbefore and hereinafter in degrees Celsius.

Example 1

4 mmol of 1-(2-p-nitrophenylethyl)-3-piperidinol [prepared from 3-piperidinol by alkylation with p-nitrophenethyl bromide or p-nitrostyrene], 4 mmol of p-nitrophenol, 4 mmol of triphenylphosphine and 4 mmol of diethyl azodicarboxylate are dissolved in 100 ml of THF and stirred at room temperature for 48 h. After the usual working up, the residue is chromatographed on silica gel using dichloromethane/methanol (99:1) and ethyl acetate/methanol (99:1) successively as mobile phases.

The following are obtained:

a) 1-(2-p-nitrophenylethyl)-2-(p-nitrophenoxymethyl)-pyrrolidine;

b) 1-(2-p-nitrophenylethyl)-3-(p-nitrophenoxy)-piperidine.

Example 2

In analogy to Example 1, starting from (-)-1-(2-p-nitrophenylethyl)-2-prolinol, the following are obtained after chromatography on silica gel using ethyl acetate/heptane (7:3) and subsequently dichloromethane/ methanol (99:1) as mobile phases:

a) (-)-1-(2-p-nitrophenylethyl)-2-(p-nitrophenoxymethyl)pyrrolidine
$[\alpha]^{20}_D$ -98.4°;

b) (+)-1-(2-p-nitrophenylethyl)-3-(p-nitrophenoxy)-piperidine
$[\alpha]^{20}_D$ +37.2°.

The following are obtained analogously

from (+)-1-(2-p-nitrophenylethyl)-2-prolinol:

a) (+)-1-(2-p-nitrophenylethyl)-2-(p-nitrophenoxymethyl)pyrrolidine
$[\alpha]^{20}_D$ +97.8°;

b) (+)-1-(2-p-nitrophenylethyl)-3-(p-nitrophenoxy)-piperidine
$[\alpha]^{20}_D$ -36.6°.

Example 3

In analogy to Example 1, starting from 1-(2-p-nitrophenylethyl)-2-hydroxymethylpiperidine, the following are obtained by reaction with p-nitrophenol with a reaction time of 60 h (purification: silica gel/methyl tert.-butyl ether and subsequently heptane/acetone (7:3))

1-(2-p-nitrophenylethyl)-2-(p-nitrophenoxymethyl)-piperidine and
1-(2-p-nitrophenylethyl)-3-(p-nitrophenoxy)-hexahydroazepine.

Subsequent reaction with fumaric acid provides after crystallization (ethyl acetate/diisopropyl ether)

a) 1-(2-p-nitrophenylethyl)-2-(p-nitrophenoxymethyl)-piperidine
m.p. (fumarate) 122°;

b) 1-(2-p-nitrophenylethyl)-3-(p-nitrophenoxy)-hexahydroazepine
m.p. (fumarate) 137°.

Example 4

In analogy to Example 1, the following are obtained by reaction of p-nitrophenol

with 1-(2-p-nitrophenylethyl)-3-hydroxymethylpiperidine (purification: silica gel/methyl tert.-butyl ether and

subsequently heptane/acetone (7:3))
1-(2-p-nitrophenylethyl)-3-(p-nitrophenoxy-methyl)piperidine;

with 1-(2-p-nitrophenylethyl)-4-piperidinol (purification: silica gel/heptane:acetone (7:3) and subsequently ethyl acetate/methanol (19:1))
1-(2-p-nitrophenylethyl)-4-(p-nitrophenoxy)-piperidine;

with (-)-1-(2-p-nitrophenylethyl)-3-pyrrolidinol (purification: silica gel/methyl tert.-butyl ether:petroleum ether:methanol (25:24:1))
(+)-1-(2-p-nitrophenylethyl)-3-(p-nitrophenoxy)-pyrrolidine, m.p. 97°,
$[\alpha]^{20}_{D}$ = +13.8° (dioxane).

Example 5

In analogy to Example 1, reaction of 1-benzhydryl-azetidine [obtainable by reaction of benzhydrylamine with 1-chloro-2,3-epoxypropane] with N-(4-hydroxyphenyl)-phthalimide results, after the usual working up, in 1-benzhydryl-3-[4-(1,3-dioxo-2-isoindolinyl)phenoxy]-azetidine
(purification: silica gel/diisopropyl ether:methanol (49:1)).

Elimination of the benzhydryl group by treatment with H_2 gas/Pd on carbon (Pd content 1 %) in toluene at room temperature provides 3-[4-(1,3-dioxo-2-isoindolinyl)-phenoxy]azetidine.

Example 6

1 mmol of 3-[4-(1,3-dioxo-2-isoindolinyl)-phenoxy]-azetidine is dissolved in 40 ml of dichloromethane, 1 equivalent of p-nitrophenethyl bromide is added, and the mixture is stirred at room temperature for 6 h. The

usual working up results in 1-(2-p-nitrophenylethyl)-3-[4-(1,3-dioxo-2-isoindolinyl)phenoxy]azetidine.

Example 7

0.9 g of 1-(2-p-nitrophenylethyl)-3-[4-(1,3-dioxo-2-isoindolinyl)phenoxy]azetidine is dissolved in 50 ml of THF, and 0.5 g of hydrazine is added. The mixture is boiled for 2 h and then worked up as usual. 1-(2-p-Nitrophenylethyl)-3-(p-aminophenoxy)azetidine is obtained.

Example 8

18 mmol of p-nitrophenol are dissolved in 15 ml of DMF, 22 mmol of NaH are added, and the mixture is stirred at 40° for 30 min. Subsequently, 18 mmol of 1-(2-p-nitrophenylethyl)-2-chloromethylpiperidine [prepared from the piperidinol derivative by halogenation with thionyl chloride/DMF in dichloromethane] are dissolved in 20 ml of DMF, added to the phenolate solution and stirred at 90° for 4 h. The solution is concentrated, the residue is taken up in toluene, and the solution is washed with 2 N sodium hydroxide solution and extracted with 2 N hydrochloric acid. The usual working up and purification by chromatography (silica gel/methyl tert.-butyl ether) results in

a) 1-(2-p-nitrophenylethyl)-2-(p-nitrophenoxymethyl)-piperidine;

b) 1-(2-p-nitrophenylethyl)-3-(p-nitrophenoxy)-hexahydroazepine.

Example 9

85 mmol of 1-(2-p-nitrophenylethyl)-2-(p-nitrophenoxymethyl)pyrrolidine are hydrogenated on 15 g of Raney Ni in 400 ml of ethanol and 40 ml of THF at 20° and 3 bar

for 7 h. The solution is concentrated and worked up as usual. 1-(2-p-Aminophenylethyl)-2-(p-aminophenoxymethyl)-pyrrolidine is obtained.

The following are obtained analogously by catalytic reduction with Raney Ni:

from 1-(2-p-nitrophenylethyl)-3-(p-nitrophenoxy)-piperidine:
1-(2-p-aminophenylethyl)-3-(p-aminophenoxy)-piperidine;

from (-)-1-(2-p-nitrophenylethyl)-2-(p-nitrophenoxy-methyl)pyrrolidine:
(-)-1-(2-p-aminophenylethyl)-2-(p-aminophenoxy-methyl)pyrrolidine;

from (+)-1-(2-p-nitrophenylethyl)-3-(p-nitrophenoxy)-piperidine:
(+)-1-(2-p-aminophenylethyl)-3-(p-aminophenoxy)-piperidine;

from (+)-1-(2-p-nitrophenylethyl)-2-(p-nitrophenoxy-methyl)pyrrolidine:
(+)-1-(2-p-aminophenylethyl)-2-(p-aminophenoxy-methyl)pyrrolidine;

from (-)-1-(2-p-nitrophenylethyl)-3-(p-nitrophenoxy)-piperidine:
(-)-1-(2-p-aminophenylethyl)-3-(p-aminophenoxy)-piperidine;

from 1-(2-p-nitrophenylethyl)-2-(p-nitrophenoxymethyl)-piperidine:
1-(2-p-aminophenylethyl)-2-(p-aminophenoxymethyl)-piperidine;

from 1-(2-p-nitrophenylethyl)-3-(p-nitrophenoxy)-hexahydroazepine:
1-(2-p-aminophenylethyl)-3-(p-aminophenoxy)-hexahydroazepine;

from 1-(2-p-nitrophenylethyl)-3-(p-nitrophenoxymethyl)-piperidine:
1-(2-p-aminophenylethyl)-3-(p-aminophenoxymethyl)-piperidine;

from 1-(2-p-nitrophenylethyl)-4-(p-nitrophenoxy)-piperidine:
1-(2-p-aminophenylethyl)-4-(p-aminophenoxy)-piperidine;

from (+)-1-(2-p-nitrophenylethyl)-3-(p-nitrophenoxyl)-pyrrolidine:
(+)-1-(2-p-aminophenylethyl)-3-(p-aminophenoxy)-pyrrolidine.

Example 10

13 mmol of 1-(2-p-aminophenylethyl)-2-(p-aminophenoxymethyl)pyrrolidine are dissolved in 40 ml of dry pyridine and, while stirring under an N_2 atmosphere and cooling in ice, at a temperature of 5-10° 39 mmol of mesyl chloride are added dropwise and the mixture is stirred at the same temperature for 2 h. Ethyl acetate is added to the solution. The resulting precipitate is separated off and taken up in ethyl acetate/$NaHCO_3$ solution. The usual working up and purification by chromatography (silica gel/dichloromethane/methanol (49:1)) results in 1-(2-p-methylsulfonamidophenylethyl)-2-(p-methylsulfonamidophenoxymethyl)pyrrolidine, m.p. 61-63°.

The following are obtained analogously by reaction with mesyl chloride:

from 1-(2-p-aminophenylethyl)-3-(p-aminophenoxy)-piperidine:
1-(2-p-methylsulfonamidophenylethyl)-3-(p-methylsulfonamidophenoxy)piperidine, m.p. 148-149°;

from (-)-1-(2-p-aminophenylethyl)-2-(p-aminophenoxymethyl)pyrrolidine:
(-)-1-(2-p-methylsulfonamidophenylethyl)-2-(p-methylsulfonamidophenoxymethyl)pyrrolidine, $[\alpha]^{20}_D$-73.9°;

from (+)-1-(2-p-aminophenylethyl)-3-(p-aminophenoxy)-piperidine:
(+)-1-(2-p-methylsulfonamidophenylethyl)-3-(p-methylsulfonamidophenoxy)piperidine, m.p. 168°, $[\alpha]^{20}_D$ +31.8°;

from (+)-1-(2-p-aminophenylethyl)-2-(p-aminophenoxymethyl)pyrrolidine:
(+)-1-(2-p-methylsulfonamidophenylethyl)-2-(p-methylsulfonamidophenoxymethyl)pyrrolidine, $[\alpha]^{20}_D$ -72.0°;

from (-)-1-(2-p-aminophenylethyl)-3-(p-aminophenoxy)-piperidine:
(-)-1-(2-p-methylsulfonamidophenylethyl)-3-(p-methylsulfonamidophenoxy)piperidine, m.p. 168°, $[\alpha]^{20}_D$ -32.7°;

from 1-(2-p-aminophenylethyl)-2-(p-aminophenoxymethyl)-piperidine:
1-(2-p-methylsulfonamidophenylethyl)-2-(p-methylsulfonamidophenoxymethyl)piperidine;

from 1-(2-p-aminophenylethyl)-3-(p-aminophenoxy)-hexahydroazepine:
1-(2-p-methylsulfonamidophenylethyl)-3-(p-methylsulfonamidophenoxy)hexahydroazepine;

from 1-(2-p-aminophenylethyl)-3-(p-aminophenoxymethyl)-piperidine:
1-(2-p-methylsulfonamidophenylethyl)-3-(p-methylsulfonamidophenoxymethyl)piperidine, m.p. 199-200°;

from 1-(2-p-aminophenylethyl)-4-(p-aminophenoxy)-piperidine:
1-(2-p-methylsulfonamidophenylethyl)-4-(p-methylsulfonamidophenoxy)piperidine, m.p. 182-183°;

from (+)-1-(2-p-aminophenylethyl)-3-(p-aminophenoxy)-pyrrolidine:
(+)-1-(2-p-methylsulfonamidophenylethyl)-3-(p-methylsulfonamidophenoxy)pyrrolidine, m.p. 199-200°, $[\alpha]^{20}_D$ +7.3° (dioxane).

Example 11

10 mmol of 1-(2-p-aminophenylethyl)-3-(p-aminophenoxy)-pyrrolidine are dissolved in 45 ml of dry pyridine and 45 ml of acetic anhydride and stirred at room temperature for 24 h. Water is added to the suspension while cooling in ice, the mixture is stirred at room temperature for 3 h, 2 N sodium hydroxide solution is added until opalescent, and the usual working up is carried out. Recrystallization from methanol results in 1-(2-p-acetamidophenylethyl)-3-(p-acetamidophenoxy)-pyrrolidine, m.p. 213-214°.

The following examples relate to pharmaceutical preparations.

Example A: Vials

A solution of 100 g of an active substance of the formula I and 5 g of disodium hydrogen phosphate in 3 l of double-distilled water is adjusted to pH 6.5 with 2 N hydrochloric acid, sterilized by filtration, dispensed into vials, lyophilized and sealed sterile. Each vial

contains 5 mg of active substance.

Example B: Suppositories

A mixture of 20 mg of an active substance of the formula I with 100 g of soya lecithin and 1400 g of cocoa butter is melted, poured into moulds and left to cool. Each suppository contains 20 mg of active substance.

Example C: Solution

A solution is prepared from 1 g of an active substance of the formula I, 9.38 g of NaH_2PO_4 x 2 H_2O, 28.48 g of Na_2HPO_4 x 12 H_2O and 0.1 g of benzalkonium chloride in 940 ml of double-distilled water. The pH is adjusted to 6.8, the volume is made up to 1 l and the solution is sterilized by radiation. This solution can be used in the form of eye drops.

Example D: Ointment

500 mg of an active substance of the formula I are mixed with 99.5 g of petrolatum under aseptic conditions.

Example E: Tablets

A mixture of 1 kg of active substance of the formula I, 4 kg of lactose, 1.2 kg of potato starch, 0.2 kg of talc and 0.1 kg of magnesium stearate is compressed to tablets in a conventional way such that each tablet contains 10 mg of active substance.

Example F: Coated tablets

Tablets are compressed in analogy to Example E and are then coated in a conventional way with a coating composed of sucrose, potato starch, talc, tragacanth and colorant.

Example G: Capsules

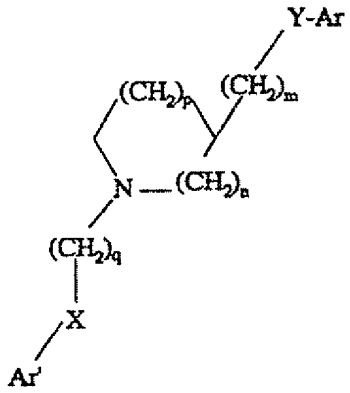
2 kg of active substance of the formula I are packed into hard gelatin capsules in a conventional way so that each capsule contains 20 mg of the active substance.

Example H: Ampoules

A solution of 1 kg of active substance of the formula I in 60 l of double-distilled water is dispensed into ampoules, lyophilized under aseptic conditions and sealed sterile. Each ampoule contains 10 mg of active substance.

Patent Claims

1. Cyclic amine derivatives of the formula I



I,

in which

Ar and Ar' are each, independently of one another, phenyl which is unsubstituted or substituted once or twice by NO_2, NH_2, Hal, CF_3, A, $NHSO_2A$ or NHAc,

X and Y are each, independently of one another, O or a bond,

m is 0 or 1,

n is 0, 1 or 2,

p is 0, 1, 2 or 3,

q is 2 or 3,

A is alkyl having 1-6 C atoms,

Hal is F, Cl, Br or I and

Ac is alkanoyl having 1-8 C atoms, aralkanoyl having 8-10 C atoms or aroyl

having 7-11 C atoms,

and their physiologically acceptable salts.

2. An enantiomer of a compound of the formula I according to Claim 1.

3. (a) 1-(2-p-methylsulfonamidophenylethyl)-3-(p-methylsulfonamidophenoxy)piperidine;

(b) 1-(2-p-methylsulfonamidophenylethyl)-2-(p-methylsulfonamidophenoxymethyl)pyrrolidine;

(c) 1-(2-p-nitrophenylethyl)-3-p-nitrophenoxypyrrolidine;

(d) 1-(2-p-acetamidophenylethyl)-3-p-acetamidophenoxypyrrolidine;

(e) 1-(2-p-methylsulfonamidophenylethyl)-3-p-methylsulfonamidophenoxypyrrolidine;

(f) 1-(2-p-nitrophenylethyl)-2-(p-nitrophenoxymethyl)piperidine;

(g) 1-(2-p-nitrophenylethyl)-3-p-nitrophenoxyhexahydroazepine;

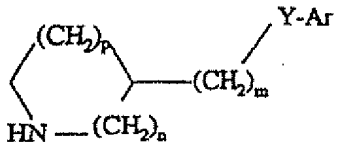
(h) 1-(2-p-methylsulfonamidophenylethyl)-2-(p-methylsulfonamidophenoxymethyl)piperidine;

(i) 1-(2-p-methylsulfonamidophenylethyl)-3-p-methylsulfonamidophenoxyhexahydroazepine;

(j) 1-(2-p-methylsulfonamidophenylethyl)-4-p-methylsulfonamidophenoxypiperidine;

(k) 1-(2-p-methylsulfonamidophenylethyl)-3-(p-methylsulfonamidophenoxymethyl)piperidine.

4. Process for the preparation of compounds of the formula I according to Claim 1, characterized in that a compound of the formula II



II,

in which

Ar, Y, m, n and p have the stated meaning,

is reacted with a compound of the formula III,

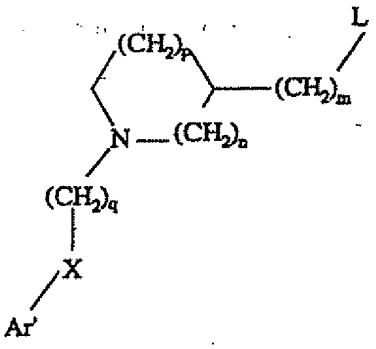
$$Ar\text{-}X\text{-}(CH_2)_q\text{-}L \qquad III,$$

in which

Ar, X and q have the stated meaning, and

L is OH, Cl, Br or a reactive, functionally modified OH group,

or in that, to prepare a compound of the formula I according to Claim 1 in which Y is oxygen, a compound of the formula IV



IV,

in which

Ar, X, L, m, n, p and q have the stated meanings,

is reacted with a compound of the formula V

$$Ar\text{-}Z \qquad V,$$

in which

Ar has the stated meaning, and

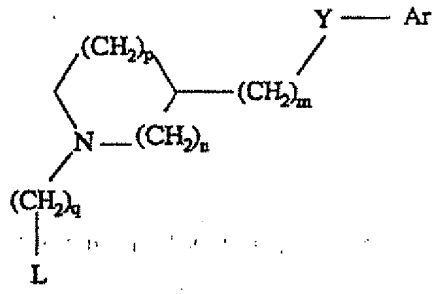
Z is OH or a reactive, functionally modified OH group, including a group with salt-like characteristics,

or in that a compound of the formula Va

$$Ar'\text{-}Z \qquad Va,$$

in which Z and Ar' have the stated meanings,

is reacted with a compound of the formula VI



VI,

in which

Ar, Y, L, m, n, p and q have the stated meanings,

or in that a compound which corresponds to the formula I but has in place of one or more CH_2 groups one or more reducible groups is converted by

reduction into a compound of the formula I, and/or in that one or both groups Ar and Ar' in a compound of the formula I are converted into other radicals Ar and Ar', respectively, and/or in that a basic compound of the formula I is converted by treatment with an acid into one of its physiologically acceptable acid addition salts.

5. Process for the production of pharmaceutical preparations, characterized in that a compound of the formula I and/or one of its physiologically acceptable salts is converted together with at least one solid, liquid or semiliquid vehicle or ancillary substance into a suitable dosage form.

6. Pharmaceutical preparation characterized by a content of at least one compound of the formula I and/or one of its physiologically acceptable salts.

7. Use of compounds of the formula I according to Claim 1 or of their physiologically acceptable salts for the production of a medicament.

8. Use of compounds of the formula I according to Claim 1 or of their physiologically acceptable salts for controlling diseases.

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